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Cefaclor, an alternative to third generation cephalosporins for the treatment of gonococcal urethritis in the developing world?

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Objective: To reassess the in vivo and in vitro efficacy of cefaclor for the treatment of uncomplicated gonococcal infection.

Design: Open clinical trial conducted in South Africa among consecutive male patients with symptoms and signs of uncomplicated urethritis and laboratory evidence of gonorrhoea.

Methods: Patients were treated with 3 g of cefaclor plus 1 g probenecid as a single dose. Urethral specimens were cultured for *Neisseria gonorrhoeae* at the initial visit and at follow up. Patients were considered cured if follow up cultures were negative. Treatment was considered to have failed in the patients infected with identical gonococcal strains at the initial and at the control visit. Those with evidence of infection at the follow up visit were administered 400 mg of ofloxacin and doxycycline 100 mg twice daily for 7 days. Minimal inhibitory concentrations (MICs) of cefaclor were determined by an agar dilution technique on the gonococcal isolates from the study subjects. The results were compared with those of isolates from three other African countries.

Results: Of 155 patients evaluated, 151 were cured (97%). Thirty per cent of the patients complained of adverse effects, mainly gastrointestinal. Even though MICs for the isolates from the three other African countries were significantly higher than those for the isolates from the study, none was considered resistant to cefaclor in vitro. MICs were markedly influenced by the type of test medium used.

Conclusion: The trial demonstrated the efficacy of a single oral dose of cefaclor with probenecid for the treatment of uncomplicated gonococcal urethritis in South Africa. Its potential as an alternative therapy to third generation cephalosporins deserves to be further investigated.

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Introduction

The third generation cephalosporins have been recommended by the WHO and CDC as first line drugs for the treatment of uncomplicated gonococcal infection. Unfortunately these antibiotics are frequently not available or are too expensive for STD patients in many countries. Resistance to cheaper alternatives such as trimethoprim-sulphamethoxazole and thiamphenicol has been detected in many developing countries; therefore, they cannot be recommended without first conducting a baseline assessment of their in vitro activity and in vivo efficacy.¹ In the early 1980s the oral second generation cephalosporin cefaclor was shown to be effective against gonococcal infection.²⁻⁴ The antibiotic has the advantage of being administered as a single oral dose and has not been associated with any major side effects. Compared with the third generation cephalosporins, cefaclor also has the advantage of no longer being under patent and could therefore be marketed at a lower price. In the studies reported here we conducted an open uncontrolled trial to reassess the efficacy of cefaclor for the treatment of uncomplicated gonococcal infection in South Africa, and compared the clinical results with the results of in vitro susceptibility tests. In addition, we

tested gonococcal isolates from three other regions of Africa for their in vitro susceptibilities to cefaclor, and compared the results with those obtained in South Africa where this clinical assessment was performed.

Materials and methods

STUDY POPULATION

The study was conducted in 1996 at the Leslie Williams' Memorial Hospital in Carletonville, Gauteng, South Africa, which caters for workers employed by the goldfields of South African mining group. Consecutive men presenting with symptoms of uncomplicated urethritis who gave written informed consent, participated in the study. All patients underwent a standardised interview concerning their present illness, history of STDs and other illnesses, as well as a routine physical examination which included the genitalia and regional lymph nodes. Individuals known or suspected to have chronic diseases, those with documented allergic reactions to β lactam antibiotics, or known to have received a systemic antibiotic therapy within 14 days were excluded from the study. A sample of urethral exudate was obtained from the urethral meatus using a sterile cotton tipped swab from

which two smears were prepared for microscopy. An endourethral swab was subsequently plated directly onto modified New York City medium at the clinic. In all, 190 patients were provisionally enrolled in the study based on the finding of typical intracellular diplococci detected on a Giemsa stained smear. These men received six 500 mg capsules of cefaclor (Ceclor, Eli Lilly), plus two tablets of 500 mg of probenecid (Benemid, Merck) as a single dose, under direct supervision.

A confirmatory Gram stain was subsequently performed on the second smear at the laboratory. All culture plates were kept in candle jars at the clinic before transportation, within 5 hours, to the central laboratory in Johannesburg, 80 km away. A definitive diagnosis of gonococcal urethritis was based on culture and biochemical identification of typical colonies of *N gonorrhoeae* growing on the selective medium.

Patients were instructed to abstain from sexual activity or to use condoms and to return after 4–14 days. (The return date was extended from 4–7 to 4–14 days by the local investigator. The follow up rate was improved while the risk of reinfection was limited.) Condoms were provided free of charge. At the control visit, patients were questioned about sexual activity, response to therapy, and possible adverse reactions to therapy. Giemsa and Gram stained smears and urethral cultures were repeated. Patients were considered cured of gonococcal urethritis if follow up urethral smear and cultures were negative. Those with positive culture were considered to be either reinfected or had failed to respond to treatment. Reinfection was differentiated from treatment failure by the isolation of different gonococcal strains at the first and control visit by using serotyping and auxotyping methods previously described.^{5,6} If there was no difference and there was no history of re-exposure, the treatment was considered to have failed. Patients with microscopic evidence of gonorrhoea at the control visit were routinely administered oral ofloxacin 400 mg immediately plus doxycycline 100 mg twice daily for 7 days. Those with post-gonococcal urethritis received doxycycline only. All findings at the first and control visit were recorded on the case report forms. The trial was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committees of

the Institute of Tropical Medicine in Antwerp, Belgium and the University of the Witwatersrand, Johannesburg.

ANTIMICROBIAL SUSCEPTIBILITY TESTING

Isolates of *N gonorrhoeae* recovered during the clinical study were subcultured onto plates containing gonococcal agar base (Gibco) supplemented with 1% haemoglobin (Gibco) and 1% IsoVitaleX (Becton Dickinson) and stored frozen at –70°C in trypticase soy broth (Gibco) containing 10% glycerol until tested. Minimal inhibitory concentrations (MICs) of cefaclor were determined by an agar dilution method on Diagnostic Sensitivity Test (DST) agar (Unipath) supplemented with 5% lysed horse blood and 1% IsoVitaleX,⁷ at the South African Institute for Medical Research in Johannesburg. Cefaclor powder of known potency was obtained from Eli Lilly Research Laboratories and dilutions of the initial solution were made to achieve final antibiotic concentrations ranging from 0.015 to 4 mg/l. Reference laboratory strains of *N gonorrhoeae* WHO A to E were included with each MIC run. All isolates from the cefaclor trial were retested at the Institute of Tropical Medicine, Antwerp, Belgium using both DST agar and GC agar base (Difco) with 1% IsoVitaleX, following the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS).⁸ A further 356 gonococcal isolates obtained from three African countries in 1995–6 (218 from Zambia, 94 from Côte d'Ivoire, and 44 from Ethiopia), were tested using the NCCLS method only. Reference laboratory strains of *N gonorrhoeae* WHO A to E and ATCC 49226 were included in each run.

STATISTICAL ANALYSIS

After logarithmic transformation the paired *t* test was used to compare the MICs obtained for the South African isolates using the DST and NCCLS techniques. The analysis of variance was used to test the difference between MICs from the four countries.

Results

IN VIVO EFFICACY TRIAL

Of the 190 original patients enrolled in the study, 18 were lost to follow up, and 10 returned later than the 14 day cut off point. An additional six had been enrolled on presumptive microscopic diagnosis but subsequently proved to be culture negative for gonorrhoea. Reinfection was assumed in three of the seven patients who were still infected at the control visit because the gonococcal strains showed completely different auxotypes, serotypes, and/or MICs before and after treatment. There was some overlap among these groups since one patient who initially entered the study proved to be *N gonorrhoeae* culture negative and also failed to return for follow up. In addition, a further patient who was reinfected also returned late for evaluation. Therefore, a total of 35 patients were excluded leaving 155 evaluable patients (table 1). Treatment was considered to have failed in the

Table 1 Results of the in vivo efficacy trial with cefaclor for gonococcal urethritis

	No	%
Patients enrolled (positive Gram stain)	190	
Returned for control	172	91
Evaluable*	155	
Reinfection†	3	
Cured	151	97 (n = 155)
treatment failure	4	
Reported adverse effects	51	30 (n = 172)
gastrointestinal	46	90 (n = 51)
haematuria	3	
urticaria	1	
headache	1	

*Ten patients returned later than 14 days after treatment, six were mistakenly enrolled, and 18 failed to return for follow up.

†Reinfected patients were excluded from the analysis.

Table 2 *In vitro* susceptibility of *N gonorrhoeae* to cefaclor in four African countries

		Minimum inhibitory concentrations (mg/l)											
Country	Method	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32
Zambia	NCCLS												
	No %*							5 2.3	35 18.3	95 61.9	77 97.2	6 100	
Côte d'Ivoire	NCCLS												
	No %							2 2.1	31 35.1	44 81.9	13 95.7	4 100	
Ethiopia	NCCLS												
	No %								3 6.8	25 63.6	12 90.9	3 97.7	1 100
South Africa	NCCLS												
	No %†				1 0.6	8 5.3	21 17.6	59 52.1	51 81.9	27 97.7	4 100		
South Africa	DST												
	No %	2 1.2	7 5.3	27 21.1	33 40.4	37 62.0	38 84.2	16 93.6	11 100				

*Cumulative percentages.

†Of 183 specimens that were shipped to Antwerp 178 were retested and 171 pairs were compared. Seven pairs were not included in the analysis because of the wide discrepancy between the laboratories, suggesting testing errors.

four patients who yielded identical strains at the initial and control visit. The cure rate obtained with cefaclor was therefore 151 of 155 (97%).

Of the 155 patients whose data were used in the analysis, 54 (35%) showed microscopic evidence of post-gonococcal urethritis (≥ 5 polymorphonuclear leucocytes per high power field) on Giemsa stained smears.

Fifty one of the 172 patients followed up (30%) reported adverse effects: the majority (90%) reported gastrointestinal symptoms, three had haematuria, one complained of urticaria, and one of headache. These side effects were self limiting and none required specific treatment.

IN VITRO SUSCEPTIBILITY TO CEFACLOR

The MICs of cefaclor to 527 isolates from four different African countries, including the strains isolated during this study (218 from Zambia, 94 from Côte d'Ivoire, 44 from Ethiopia, and 171 from South Africa) are shown in table 2. Isolates from Zambia, Côte d'Ivoire, and Ethiopia had a MIC₅₀ of 4 mg/l, and a MIC₉₀ of 8 mg/l. In contrast, values observed with the South African isolates were lower, with a MIC₅₀ and a MIC₉₀ of 1 mg/l and 4 mg/l respectively. The differences in MIC values between the different countries were statistically significant ($p < 0.001$).

The MICs for the strains obtained from the four patients who failed to respond to their treatment were typical of the tested population, with values between 1 and 4 mg/l. Still, if the NCCLS approved MIC breakpoints for *Haemophilus influenzae* are to be accepted for *N gonorrhoeae* (that is, MICs ≤ 8 mg/l = susceptible, > 32 mg/l = resistant), none of the 527 isolates would be considered resistant to cefaclor *in vitro*.

One unexpected finding was the marked difference in MICs observed as a consequence of the methods used. The MICs recorded for the 171 isolates that were tested by both methods are shown in table 2. When using the DST method, all isolates except two had lower MICs than when the same isolates were tested with the NCCLS method. The MIC₅₀ was 0.25 mg/l and the MIC₉₀ was 1 mg/l when using the DST method, while these values

were 1 mg/l and 4 mg/l respectively when using the NCCLS method. The difference between the 171 pairs was highly significant ($p < 0.001$).

Discussion

The cure rate recorded for cefaclor in this open trial was 97%. This was similar to the results of other published efficacy studies conducted in the late 1970s and early 1980s, suggesting that cefaclor may be a valuable alternative for the treatment of uncomplicated urogenital gonorrhoea in countries with limited health resources, especially in a situation of growing resistance to the fluoroquinolones.⁹ Panikabutra *et al* published a cure rate of 90% when cefaclor was administered as a 3 g single dose alone in Bangkok, Thailand, and of 96% when 3 g cefaclor and 1 g probenecid were administered jointly, although the difference between the two groups was not statistically significant.² Tupasi *et al* reported a 93% cure rate in 61 female patients with uncomplicated gonococcal infection who were given 3 g single dose with probenecid in Manila, Philippines.³ Finally, Spagna *et al* reported a cure rate of 98% in a study undertaken in Columbus, Ohio, but with a multiple dose treatment regimen.⁴ Cefaclor and cefixime share the advantages of single oral administration, absence of toxicity in pregnancy, and lack of serious side effects. However, being a generic drug cefaclor could be marketed at a substantially lower price than cefixime.

Since cefaclor has no activity against either *C trachomatis* or the genital mycoplasmas the rate of PGU detected during this study (35%) is similar to rates previous recorded with single dose treatment using β lactam antibiotics. Under these circumstances the use of cefaclor in combination with multidose tetracycline/doxycycline therapy would therefore be advocated in settings where syndromic management of acute urethritis is practised.

Nevertheless, the 30% rate of adverse effects reported in this trial is a matter for concern. There was no association between side effects and HIV status—testing had been carried out in these patients for another study protocol. Adverse effects were reported by 19

of the 50 HIV positive patients, and by 43 of the 122 HIV negative patients ($p = 0.6$). As anticipated, patients complained mainly of gastrointestinal symptoms. The six cefaclor and two probenecid tablets were administered with a single glass of water, and some patients had not eaten for several hours. The administration of cefaclor with food might lessen gastrointestinal effects, but food is also said to reduce the intestinal absorption rate and subsequently the maximum serum concentration.¹⁰ Haematuria has not been reported in earlier trials with cefaclor.²⁻⁴ Haematological reactions are known to occur with other cephalosporins, though very infrequently.¹¹ No side effect was so serious that treatment was required, but if confirmed, the frequency of their occurrence might affect treatment acceptability.

In studies undertaken in the late 1970s and early 1980s, the in vitro susceptibility ranges of *N gonorrhoeae* to cefaclor were shown to be quite broad.^{2-4 12 13} In Hall *et al*'s study the MIC₅₀ was only 0.09 mg/l and 0.19 mg/l for nPPNG and PPNG isolates respectively, but in Panikabutra's survey it was as high as 2 mg/l and 4 mg/l for nPPNG and PPNG isolates respectively. Likewise, the MIC₉₀ was as low as 0.4 mg/l in Spagna's study, but as high as 4 mg/l for nPPNG and 8 mg/l for PPNG in Thailand. The MIC values for the isolates from Zambia, Côte d'Ivoire, and Ethiopia recorded here were slightly higher than those detected in Thailand in 1983, which are the highest reported in the literature to date. At present, there are no MIC breakpoints for cefaclor recommended by the NCCLS with *N gonorrhoeae*. Based on the MIC breakpoints for *Haemophilus influenzae*, none of the 527 isolates in our study could be considered resistant to cefaclor. However, because of the marked difference in the susceptibility profile to cefaclor between the South African isolates and those from the three other African countries, we might suspect cefaclor to be less effective in regions of Africa where higher MICs of cefaclor are detected.

Lastly, our study highlighted the impact of the susceptibility testing technique on the MICs of cefaclor. With the NCCLS method, all isolates except two had higher MICs than the corresponding isolates when tested by the DST method. Differences in media have long been shown to affect the MICs of penicillin, tetracycline, and erythromycin.^{7 14} It appears that cefaclor should be added to this list. At the present time no consensus has been reached regarding standardisation of protocols for susceptibility testing of *N gonorrhoeae*. However, since surveillance for gonococcal antimicrobial resistance is now an interna-

tional issue, we advocate that a single standard protocol be defined. In the meantime, one should be aware of the influence of the testing method on the MICs when comparing data between laboratories.

In summary, this trial demonstrated the efficacy of a single oral dose of cefaclor with probenecid for the treatment of uncomplicated urogenital infection with *N gonorrhoeae* in South Africa. It also demonstrated the potential of cefaclor as an alternative therapy in countries where financial constraints proscribe the recommendation of third generation cephalosporins. However, further investigation of its efficacy is warranted before it can be recommended unquestionably.

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